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Is There a Connection between Carbon Monoxide Exposure and Hypertension?

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Exposure to carbon monoxide in our society is a frequent occurrence, from auto exhaust, industrial effluents, and cigarette smoke, and takes place over a wide range of concentrations. It has been suggested that chronic CO inhalation may alter blood pressure, even possibly provoking hypertension by acting alone or in combination with other environmental stressors. Some studies examining the response to CO exposure have reported decreases in blood pressure, whereas others have found increases or no change. Blood pressure in long-term cigarette smokers is generally decreased relative to nonsmokers, albeit a slight decrease. The strength of this finding is somewhat clouded by the effect of the lower body weight in smokers. The increases in blood pressure observed acutely with smoking are mainly due to nicotine. Chronically, the hypertensive action of nicotine is largely offset by the hypotensive action of CO. Several studies support the notion that environmental CO exposure or smoking accelerates or exacerbates hypertension in some people. It has been asserted that chronic CO exposure increases the development of atherosclerotic disease; however, convincing evidence from animal experiments is lacking. Nevertheless, CO may elevate plasma cholesterol and does appear to enhance atherosclerosis when serum cholesterol is greatly elevated by diet. Using the borderline hypertensive rat, an animal model reputed to have increased sensitivity to environmental stimuli, we found no evidence to suggest a provocatory role for CO in the development of hypertension; instead, CO exposure produced hypotension. On the whole, the human and animal literature, as well as our studies, fail to support the hypothesis that long-term CO exposure is capable of provoking an increase in blood pressure, even in borderline hypertensive or sensitive individuals.

Introduction

Carbon monoxide is a product of the incomplete combustion of carbonaceous substances. Human exposure to CO in our society is frequent and takes place over a wide range of concentrations. It derives mainly from auto exhaust, industrial effluents, and cigarette smoke. In underdeveloped countries, fumes from heating and cooking equipment are far more important CO sources. CO levels in the open air may reach 50 to 100 ppm, or even higher on occasion, and in certain locations may result in carboxyhemoglobin (COHb) saturations of 5 to 12% or above (*1*). Cigarette smoke contains 30,000 to 50,000 ppm CO and, depending upon smoking frequency and the extent of inhalation of the smoke, can produce up to 12 to 14% COHb (*2*).

Hypertension is a major health problem in the western world, with approximately 20% of the population showing borderline to severe high blood pressure. Hypertension is a well-recognized risk factor for coronary heart disease, heart failure, and stroke. Despite the enormous human exposure to CO, few studies have examined the possible contributory role of CO in the development of hypertension. Based upon the studies that have been done, it would appear that CO is not an important factor in hypertension in the general population. Nonetheless, there may be individuals within the population who display heightened sensitivity to CO in terms of blood pressure. For example, those individuals with mildly elevated blood pressure (i.e., borderline hypertensives) are usually younger and tend to have an elevated cardiac output. This contrasts with people with established hypertension, for whom elevated total peripheral resistance is the rule. Borderline hypertensives are frequently those people in which only one parent shows frank hypertension. They are also reported to have reduced baroreceptor sensitivity compared to normotensives (*3*), as well as elevated plasma catecholamines and renin activity (*4*), suggesting some degree of neural hyperactivity.

The following discussion reviews the effects of CO exposure on blood pressure, both when administered as a pure gas added to air and as a component of cigarette smoke. Because atherosclerosis may also contribute to producing hypertension, the possible role of CO inhalation in the development of atherosclerosis is critically assessed. Both animal and human studies are examined. Finally, the summary results of a recent study with the borderline hypertensive rat (BHR) are presented, an experiment in which the hypothesis that chronic CO exposure may provoke hypertension was tested. For a discussion of the general cardiovascular effects of CO, several other reviews should be consulted (*5–8*).

Carbon Monoxide and Blood Pressure

The response to CO in the Sprague-Dawley rat has been thoroughly studied by Penney and his collaborators (*6–16*). The response consists of systemic arterial hypotension (Table 1) and

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Table 1. Blood pressure response to chronic carbon monoxide exposure.

Species[a]	CO concentration, ppm	Duration	Response	Reference
Rat (SHR)	500	27 days	Decrease	(16)
Rat (S-D)	500	27–42 days	Decrease	(15)
Rat (Dahl, +NaCl)	500	63 days	Increase	(17)
Rabbit	1500	10+ weeks	Increase	(20)
Rabbit	100	2500 hr	Increase	(19)
Goat	160–200	2 weeks	No change	(21)
Dog	1000	1 year	No change	(22)
Monkey	(11.2% COHb)	8 months	No change	(23)
Human	(12% COHb)	8 days	No change	(24)
Human	? (foundry)	Months–years	Slight increase	(25)

[a]SHR, spontaneously hypertensive; S-D, Sprague-Dawley.

reduced systemic vascular resistance. This occurs even though stroke volume and heart rate are elevated (9). The changes are observed at COHb levels as low as 5%. At the same time, polycythemia, expanded blood volume, and cardiac hypertrophy develop in response to CO hypoxia (10–12) in a dose-dependent manner (13,14) (e.g., polycythemia is apparent even after chronic exposure to 100 ppm CO). CO does not produce pulmonary vascular hypertension. The rapid elimination of CO, as occurs upon return to room air, causes a transient elevation of vascular resistance and blood pressure (1–2 days), while stroke volume and heart rate return to normal values (15). Reduced arterial blood pressure has also recently been demonstrated in the spontaneously hypertensive rat (SHR) during chronic exposure to CO (16).

In contrast, a study with the Dahl salt-sensitive rat fed a diet containing 8% NaCl found that 500 ppm CO exposure for 62 to 63 days enhanced development of systemic hypertension (17). It was suggested that this came about as the result of CO raising cardiac output at the same time that high dietary sodium was elevating peripheral resistance. This explanation, however, fails to recognize the fact that CO lowers peripheral vascular resistance (9). Other common air pollutants such as ozone and sulfur dioxide do not produce hypertension in this rat model (18), suggesting that the effect of CO is specific, or at least that it is due to hypoxia.

Truhaut et al. (19) found that the blood pressure of rabbits was higher following 100 ppm CO exposure for 2500 hr. A similar result was obtained by Kubota (20) in rabbits after inhalation of 1500 ppm CO for 3 hr each day for many weeks. In the latter case, the elevated blood pressure failed to renormalize after exposure when CO treatment exceeded 7 weeks.

In contrast, James et al. (21) saw no significant change in peak left ventricular pressure and total peripheral resistance in conscious goats maintained at 20% COHb for 2 weeks. Likewise, Lillehei and associates (22) found normal blood pressure in dogs gradually acclimatized to 1000 ppm CO for 6 to 8 hr per day for 1 year. No change in blood pressure was observed in cynomolgus monkeys after 8 months at 11.2% COHb (23).

As in rats, acute CO exposure has been shown to decrease peripheral resistance in humans (26). This probably results from the relaxation of vascular smooth muscle involving mechanisms postulated to be active in the local control of blood flow (e.g., adenosine release), and/or the inhibition of reflex sympathetic vasoconstrictor fibers usually activated by hypoxia. CO may also act to reset the baroreceptor reflex or to alter reflex gain, a condition found in borderline hypertensives (3). In addition, CO could act to modify neural output long term, as by increasing catecholamine outflow, which it is known to do acutely (6).

During chronic CO exposure, Klausen et al. (24) found no changes in systolic and diastolic blood pressure in resting men maintained at 12% COHb for 8 days. The former pressure increased and the latter fell relative to men working while breathing air when the men inhaling CO also worked. In acute exposures, Aronow et al. (27) failed to find changes in systolic and diastolic arterial blood pressures in patients acutely inhaling 150 ppm CO. In contrast, the systolic and diastolic blood pressures of foundry workers exposed to CO (and other gases) were found to be slightly higher than those of unexposed workers when age and smoking habits were taken into consideration (25). A 1980 epidemiologic study attempted to relate elevated urban CO concentration and the greater incidence of hypertension in city dwellers who were close relatives of village dwellers (28). Unfortunately, other factors present in the urban environment such as noise, crowding, etc., may also act to alter blood pressure.

In summary, the blood pressure response to chronic exposure to pure CO gas as reported in a number of animal and a few human studies is mixed, with some studies finding increases, some decreases, and some no change.

Cigarette Smoking and Blood Pressure

Acute Exposure

Cigarette smoking has been shown to acutely raise blood pressure and heart rate and to decrease the skin temperature of the fingers and toes (29) (Table 2). Herxheimer et al. (30) found that while inhalation of smoke from filter tip cigarettes and of nicotine aerosol produced increases in heart rate and blood pressure in healthy subjects, inhalations from nicotine-free cigarettes (i.e., dried lettuce leaves) and of aerosol propellant alone had no effect on the circulation. Similar observations have been made by others (31), suggesting that nicotine, not CO, is the active ingredient in cigarette smoke.

Table 2. The blood pressure response to cigarette smoking.

Response	Subjects	Condition	Reference
Increase	Normotensive	Acute	(29)
Increase	Normotensive	Acute	(32)
Increase	Hypertensive	Acute	(49)
No change[a]	Normotensive	Acute	(30)
No change[a]	Normotensive, CHD[b]	Acute	(31)
Increase	Hypertensive	Acute and chronic	(50)
Decrease	Normotensive	Chronic	(43)
No change	Normotensive	Chronic	(34)
Decrease	Normotensive	Chronic	(35)
Decrease	Normotensive	Chronic	(36)
Decrease	Normotensive	Chronic	(37)
Decrease	Normotensive	Chronic	(38)
No change	Normotensive	Chronic	(41,42)
Decrease	Normotensive	Chronic	(39)
Decrease	Normotensive	Chronic	(40)
Decrease	Pregnant	Chronic	(45)
Decrease	Normotensive	Chronic	(46)
Decrease	Normotensive	Chronic	(44)
No change	Normotensive	Chronic	(47)
Decrease	Normotensive	Chronic	(48)
No change	Hypertensive	Chronic	(51)
Malignant hypertension	Hypertensive	Chronic	(52)
Malignant hypertension	Hypertensive	Chronic	(53)
Accelerated hypertension	Hypertensive	Chronic	(54)

[a]Nicotine-free cigarettes.
[b]CHD, coronary heart disease.

Aziz et al. (*32*) delineated two quite different groups of subjects among smokers and nonsmokers. Normoreactors showed modest increases in blood pressure (6–10 mm Hg) and heart rate (6–7 beats/min) after smoking two cigarettes; hyperreactors showed responses two to three times as large. This was also true to a lesser extent with respect to urinary total free catecholamines. Nicotine infusion was found to elevate blood pressure and cardiac output in deoxycorticoserone acetate (DOCA)-salt treated, uninephectomized rats, but failed to do so in rats ingesting a normal salt diet (*33*).

Chronic Exposure

Dawber et al. (*34*) found no association of either blood pressure or relative body weight with cigarette smoking in the Framingham study population (Table 2). Thomas (*35*) found slightly lower diastolic blood pressures and higher heart rates in smokers than in nonsmokers. Blackburn and co-workers (*36*) found lower blood pressures and higher heart rates among smokers than nonsmokers and a tendency for smokers to be leaner than nonsmokers. In contrast, Bronte-Stewart (*37*) found no significant difference in blood pressure in smokers and nonsmokers of Capetown, South Africa, although smokers tended to have a slightly lower blood pressure.

Smokers in a Tecumseh, Michigan, population had lower diastolic blood pressures, weighed less, and had faster heart rates than nonsmokers (*38*). Jenkins et al. (*39*) found that smokers in the Western Collaborative Group Study had lower blood pressures and weighed less than nonsmokers. Andrus and co-workers (*40*) reported that both systolic and diastolic blood pressures were negatively correlated with smoking in a study carried out in King City, California.

Reid et al. (*41,42*) found lower blood pressures in smokers in both America and Great Britain, but this could be largely accounted for by the lower body weights among the smokers. Lower blood pressure was also found in a Finnish study of cigarette smokers (*43*). In this study the smokers were leaner than the nonsmokers. This blood pressure difference was confirmed in a survey of 5249 middle-aged male cigarette smokers in Scandinavia (*44*). The difference could not be explained by group differences in age, body weight, or physical fitness. An association of lower blood pressure and smoking has been reported in pregnant women (*45*).

Seltzer (*46*) reported lower mean blood pressure and body weight for current cigarette smokers as compared to nonsmokers and former smokers. In an analysis of changes in the Framingham population related to the cessation of smoking, Gordon et al. (*47*) found there were only trivial changes in blood pressure in both directions, but that men gained weight after quitting. In a study of 10,000 Israeli men (*48*), it was revealed that smokers weighed less and had lower systolic and diastolic blood pressures.

Ballantyne et al. (*51*) found no relationship between cigarette consumption and either systolic or diastolic blood pressure in hypertensive patients. In contrast, Freestone and Ramsay (*50*) found that mean blood pressure was substantially lower in hypertensives after abstaining from cigarettes and coffee overnight. Smoking two cigarettes (3.4 mg nicotine) elevated blood pressure by 10/8 mm Hg, but for only 15 min, whereas drinking coffee (200 mg caffeine) elevated blood pressure by up to 10/7 mm Hg for 1 to 2 hrs. Similar results were obtained in thiazide-treated patients. Baer and Radichevich (*49*) agreed and extended these findings, reporting acutely increased heart rate, blood pressure, plasma adrenal corticotropic hormone, cortisol, and catecholamine levels in 19 hypertensive patients after smoking.

According to Isles et al. (*52*), the chance of a hypertensive patient who smokes having the malignant phase of hypertension is 5-fold that of a hypertensive patient who does not. Bloxham et al. (*53*) also suggest a relationship between cigarette smoking and malignant hypertension. Elliot and Simpson (*54*) found an excess of accelerated hypertension in hypertensive patients who smoked. There was no difference in the smoking or drinking habits of the patients with benign hypertension and those with accelerated hypertension.

Based on data from a large number of studies, it is clear that, on the average in normotensive subjects, cigarette smoking lowers blood pressure, albeit slightly, as well as body weight (*55*). Cigarette smoking also increases heart rate. It is not clear whether the lower blood pressure is due to decreased body fat or whether it is due to an independent effect of smoking. The tendency for ex-smokers to gain weight indicates that the body weight difference is not inborn, but is an effect of smoking. The acute increases in blood pressure seen with smoking are probably due to nicotine. Over the long term, the hypertensive effects of nicotine are probably largely offset by the hypotensive effects of CO.

In hypertensive subjects, in contrast, cigarette smoking appears to elevate blood pressure. The finding by Aziz et al. (*32*) of two quite different groups when exposed acutely to cigarette smoke, normoreactors and hyperreactors, is consistent with this notion. As suggested by Elliot and Simpson (*54*), although smoking cannot be considered the primary cause of hypertension, it may accelerate the condition. Thus, smoking may predispose some individuals to hypertension, possibly those with borderline hypertension or those with special sensitivities to environmental stress.

Carbon Monoxide and Atherogenesis

Epidemiologic studies have linked cigarette smoking with an increased incidence of atherosclerosis of the coronary arteries and other major blood vessels. It has been alleged that, of the many constituents of tobacco smoke, CO is the major causative agent, its mode of action being to increase the deposition of lipoprotein cholesterol in the arterial wall. Others have pointed to other components of cigarette smoke as the probable culprit. Wald et al. (*56*), for example, in a study of 1085 volunteers working in Copenhagen, reported that smokers in whom COHb was greater than 5% were 21 times more likely to develop atherosclerosis than were those in whom COHb was less than 3%. The production of atherosclerosis by CO could contribute to the long-term alteration of blood pressure, i.e., contribute to the development of hypertension.

Reviewed below are a number of animal CO-exposure studies relating to atherosclerosis that were conducted with the pure gas. We have chosen not to evaluate studies carried out with tobacco smoke. The literature clearly points out the fact that species vary widely with respect to their susceptibitily to induction of atherosclerosis in the presence of CO, with or without added dietary cholesterol, and that the results of a number of early studies carried out in a less than ideal fashion have since had to

be set aside. Several older reviews may be consulted on this topic (*57–60*).

Astrup et al. (*61*) reported that the degree of aortic atheromatosis and the content of total cholesterol in aortic tissue was significantly higher in rabbits exposed to 200 to 350 ppm CO and fed 2% cholesterol than in controls (Table 3). In later experiments (*75*), the effects were found to be greater with intermittent than with continuous CO exposure. It should be noted that the serum cholesterol levels attained in these studies were far higher than seen in most humans (800–2000 mg/dL). Even in CO-exposed rabbits (11% COHb) fed a normal diet for 3 months, aortic changes were supposedly identified by light microscopy as atherosclerosis, which were not seen in controls (*62*). No macroscopic intimal changes were seen, however. Kjeldsen et al. (*75,76*), using the electron microscope, reported local areas of partial or total necrosis of myofibrils, intimal and subintimal edema, and fibrosis in rabbits fed a normal diet and exposed to 180 ppm CO continuously for 2 weeks. A higher incidence of intimal changes was found in rabbits exposed to 180 ppm CO for 4 hr or more than in those in which the CO exposure was shorter or involved a lower CO concentration (*64*). None of these studies, however, were carried out in a blind manner.

In other studies, mild atherosclerotic lesions were observed in the aorta and the coronary and renal arteries of adult rabbits exposed to 300 to 500 ppm CO for 4 to 6 months; addition of 2% cholesterol to the diet caused more severe and widespread lesions (*63*). Unfortunately, the study did not include adequate controls. Davies et al. (65) confirmed this finding in rabbits fed 2% cholesterol for 10 weeks and in which the COHb concentration was 20% during the exposure periods. The CO exposure did not further elevate plasma or aortic cholesterol. In contrast, when noncholesterol-fed rabbits were exposed to 200, 2000, or 4000 ppm CO repeatedly for brief periods, no evidence of coronary or aortic vessel disease could be demonstrated (*66*).

Armitage et al. (*67*) found that CO (10% COHb) exposure for 6 hr per day had no enhancing effect in normocholesterolemic white carneau pigeons; however, in hypercholesterolemic birds, the severity of coronary artery atherosclerosis was significantly greater in birds exposed to CO. Turner et al. (*68*), also using white carneau pigeons, found that the incidence and severity of coronary artery disease was associated with intermittent exposure to 150 ppm CO or higher when the birds were fed 0.5% and 1.0% dietary cholesterol. With 1.0% dietary cholesterol the response was related to the close of CO. Although Astrup et al. (*61*) reported that exposure to low levels of CO increased aortic total cholesterol content in rabbits fed a high cholesterol diet, it was later found that this may have resulted from differences in serum cholesterol between the exposed and nonexposed groups (*77*).

A number of studies, reviewed by Topping (*78*), suggest that CO is capable of damaging the endothelium of arteries. This could facilitate the deposition of cholesterol in the intima and exacerbate the development of atherosclerosis. For example, endothelial permeability is increased by CO (*79*). Parving et al. (*80*) reported that CO exposure increased the transcapillary escape route of radiolabeled albumin from the blood. The *in vitro* perfusion of human coronary arteries with blood containing 15% COHb was found to increase the vessel wall uptake of [^{3}H]cholesterol (*81*). This is consistent with the findings of others (*80,82*).

Marshall and Hess (*83*) found that exposure of minipigs to 160, 185, and 420 ppm CO for 4 hr daily led to increased platelet aggregation. Increased platelet stickiness was noted in rabbits exposed to 400 ppm CO (*84*). While light microscopy revealed no changes in the arterial wall, scanning electron microscopic examination showed adhesions of shape-changed platelets on the arterial endothelium, in some cases after only a single 4-hr exposure to CO. In contrast, CO is reported to inhibit the release of adenosine diphesphate and serotonin by platelets (*85*), actions that slow platelet aggregation (*86*).

At concentrations of 200 to 300 ppm, CO was found to aggravate atherosclerosis in the coronary arteries of squirrel monkeys fed a cholesterol-containing diet for 7 months; this was not the case, however, in the aorta (*70*). After only 2 weeks of exposure to 250 ppm CO, Thomsen (*71*) reported seeing endothelial edema and other ultrastructural changes indicative of atherosclerotic vascular disease in monkey coronary arteries. In contrast to these observations, Sultzer (*69*) found that the thickness of coronary artery intimal lesions was not increased in pigs exposed to 100 ppm CO for 4 months and fed an atherogenic diet.

Theodore and his associates (*72*) detected no atheromatous changes in the aortas of monkeys, baboons, dogs, and rodents exposed to CO (32–40% COHb) for 168 days and fed standard chow. No aortic or coronary atherosclerosis was detected in cynomolgus monkeys intermittently exposed to CO (21% COHb maximum) for 14 months, either after being fed a normal diet or when fed a diet containing added cholesterol (*73*). In a like fashion, Bing and his colleagues (*74*) found no association between CO exposure and development of atherosclerosis in the same spicies of monkey intermittently exposed to 200 to 400 ppm CO for 12 months.

Despite the claims of early studies, there remains no convincing evidence that chronic CO exposure increases the risk of developing clinically significant atherosclerotic disease (*58,60*), although in some experimental models CO tends to elevate serum cholesterol (*59*). Only when serum cholesterol is artificially and greatly elevated by dietary supplementation does CO exposure appear to enhance atherosclerosis. The evidence for

Table 3. A role for carbon monoxide in atherosclerosis?

Atherosclerosis	Subjects	CO concentrations, ppm	Added dietary cholesterol	Reference
Yes	Rabbit	200–350	Yes	(*61*)
Yes	Rabbit	(11% COHb)	No	(*62*)
Yes	Rabbit	300–500	No and yes	(*63*)
Yes	Rabbit	180[a]	No	(*64*)
Yes	Rabbit	(20% COHb)[a]	Yes	(*65*)
No	Rabbit	200,2000,4000[a]	No	(*66*)
No	Pigeon	(10% COHb)[a]	No	(*67*)
Yes	Pigeon	(10% COHb)[a]	Yes	(*67*)
Yes	Pigeon	150[a]	Yes	(*68*)
No	Pig	100[a]	Yes	(*69*)
Yes	Monkey	100–300[a]	Yes	(*70*)
Yes	Monkey	250	No	(*71*)
No	Monkey dog baboon rodents	(32–40%COHb)	No	(*72*)
No	Monkey	(21% COHb)[a]	Yes	(*73*)
No	Monkey	200–400[a]	No	(*74*)

[a]Intermittent.

CO-induced atherogenesis in normocholesterolemic pigeons, swine, and primates is particularly unconvincing. In the rabbit, however, CO exposure alone may stimulate atherosclerosis.

Effects of Carbon Monoxide Exposure in a Model System

To examine the effects of chronic CO exposure on blood pressure, and particularly with regard to individuals having borderline high blood pressure and/or an enhanced sensitivity to environmental stress, an appropriate animal model was sought. The BHR, a relatively new animal, was chosen for this purpose. The BHR is the F_1 progeny of an SHR female and a normotensive Wistar Kyoto (WKY) male. The BHR is reported to be sensitive to various environmental stimuli such as shock, cold, restraint, and dietary salt (*87*), rapidly developing frank arterial hypertension compared to unstressed littermates. It was the intent of the study to determine whether chronic CO exposure, with or without the presence of another stressor (i.e., salt ingestion), would provoke hypertension in this species, and once provoked whether hypertension would persist (*88*).

Three different age groups of male BHR were used. Systolic blood pressure and heart rate measurements were begun at 62, 83, and 115 days of age, using the tail-cuff method (*9*). The study design is shown in Figure 1. The three study groups were designated as "young," "intermediate," and "old" BHR. Beginning at 62, 103, and 172 days of age, the rats in each study were randomly assigned to one of two groups, one group thereafter receiving powdered chow containing 8.8% NaCl, the other receiving standard chow (0.8% NaCl). At 80, 122, and 201 days of age, each of the high-sodium groups and the low-sodium groups were again randomly assigned, one-half for exposure to CO, the other half to remain in room air (air). Thereafter, each study contained four groups; *a*) no salt/air, *b*) no salt/CO, *c*) salt/air, and *d*) salt/CO. Each group in each study contained six to eight rats. CO exposure and the high sodium diet were terminated 28 to 31 days later. The rats remained in room air until sacrifice.

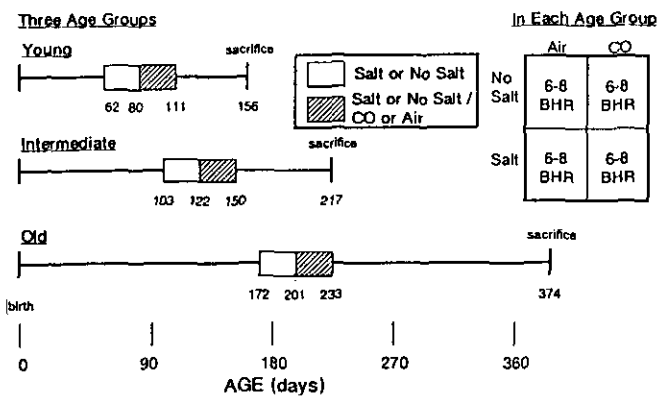

FIGURE 1. Design of the study examining the responses of young, intermediate age, and old borderline hypertensive rats (BHR) to chronic 500 ppm carbon monoxide exposure, a high salt (8.8%) diet, and a combination of chronic 500 ppm carbon monoxide exposure and a high salt (8.8%) diet. The heavy horizontal lines indicate periods before and after salt/carbon monoxide treatment.

The rats, housed in plastic shoe-box cages, were continuously exposed to 500 ppm CO (COHb = 40%) in large, transparent plastic bags inflated by an air-CO mixture (*88*). The flow rate through each bag was approximately 25 L/min to ensure rapid removal of waste gases. CO concentration was monitored by a Beckman infrared gas analyzer. Hematocrit was determined in triplicate by the microhematocrit method.

Ingestion of the high-sodium diet increased water consumption by 50 to 80% in the old study group before CO exposure. The rate of weight gain was slowed in the intermediate and old BHR, while body weight gain of the two no salt groups increased steadily. This indicates that salt ingestion at 11-fold the normal amount constituted a significant stress on the animals, although lower body weight gain of the salt-treated rats may have reflected lower food consumption due to the poor palatibility of the high salt diet. CO exposure had no effect on body weight gain.

Systolic blood pressure increased modestly with age in both the young and intermediate groups, but tended to remain constant in the old group (Fig. 2). The addition of 8 percent NaCl to the diet had no signigicant effect on blood pressure in any of the three study groups, with one exception (intermediate age salt/air group). In this instance however, blood pressure was not elevated during an earlier period of salt treatment. Exposure to CO resulted in significant decreases in blood pressure in all three study groups. The changes were of about the same magnitude regardless of age (i.e., 10–16 mm Hg) and were not modified by the presence of salt. Blood pressure recovered to control levels within 1 to 2 weeks after terminating CO exposure. Exposure to CO resulted in no long term alteration of blood pressure after exposure to CO, with or without salt, with one exception (old no salt/CO group). In this case the elevation of blood pressure was statistically significant ($p < 0.05$), but small (8 mm Hg). Neither salt nor CO, separately or in combination, had a significant effect on heart rate in any of the three study groups, either during or after CO and /or salt treatment.

Hematocrit was increased from approximately 53 to 70% in all three study groups by exposure to 500 ppm CO for 4 weeks. With one exception, the presence of salt did not modify the polycythemic response to CO. In the young group, hematocrit was 2.7% lower ($p < 0.05$) in the rats receiving salt and CO than in rats only exposed to CO. Hematocrit returned to or slightly below the control values after terminating CO exposure.

In summary, this study demonstrated that blood pressure is not elevated during or after chronic CO exposure in the BHR, with or without concurrent salt treatment. Age at the time of CO and salt treatment does not alter the blood pressure response. CO exposure significantly lowers blood pressure during the period of exposure.

Our results contrast sharply with those of Shiotsuka et al. (*17*), which was discussed above. They reported that 500 ppm CO exposure for 62 to 63 days enhanced development of systemic hypertension in the Dahl salt-sensitive rat fed a diet containing 8% NaCl. The degree of hypotension we found in the BHR was similar to that seen in previous studies with the Sprague-Dawley rat (*89*) and the SHR (*16*). There may be major physiological differences between the Dahl rat and the BHR.

The failure to observe an elevation in blood pressure in rats ingesting the high-sodium diet is inexplicable because the parents were procured from the same breeding unit, and the BHR tested were of the appropriate age and received exactly the same sodium

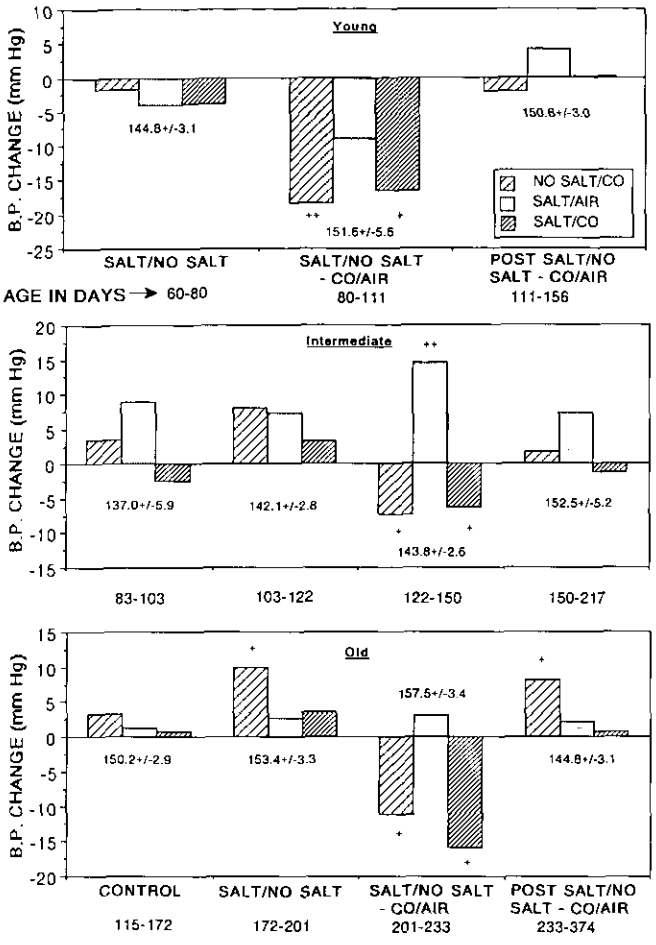

FIGURE 2. Systolic blood pressure changes (relative to an untreated control group) of young, intermediate age, and old borderline hypertensive rats (BHR) treated with a high salt (8.8%) diet, exposed to 500 ppm carbon monoxide (CO) for approximately 30 days, and allowed to recover in room air while ingesting a low salt (0.8%) diet. Control is the period before salt and CO treatment; salt/no salt - CO/air is the period when salt and CO treatment took place; post salt/no salt - CO/air is the period when salt and CO treatments were discontinued. Age during each measurement period is given below each panel. Note that there was no control period for the young group because they were too small at that time to obtain measurements with the tail cuff. Numbers below the vertical bars are control values ±SE of the mean. Compared to the control value: (+) $p < 0.05$; (++) $p < 0.01$..

supplement as in previous studies reporting increased blood pressure (*90,91*). The method of blood pressure measurement was identical to that used in previous studies. The high-sodium diet appeared to be stressful as indicated by the increased water uptake and reduction in body weight gain.

Conclusions

Animal studies examining the acute and chronic responses to CO exposure yield no clear-cut pattern in terms of arterial blood pressure. The paucity of good chronic human studies is not helpful in this regard. In general, cigarette smoking lowers blood pressure slightly in normotensive subjects, whereas there is some evidence that CO raises blood pressure in hypertensives and/or accelerates the development of malignant hypertension. A careful examination of the available animal studies reveals no convincing evidence that CO exposure in normocholesterolemic subjects increases the risk of atherosclerotic disease. Thus, atherogenic-related hypertension is probably not a function of long-term CO exposure.

Finally, by using a model system reputed to have increased sensitivity to environmental stimuli, we have found no evidence to suggest a provocatory role for CO in the development of immediate or persistent hypertension. Instead, CO exposure produced marked hypotension, followed by normal blood pressure upon terminating CO exposure. As far as human hypertension is concerned, the BHR data fail to support the hypothesis that long-term CO exposure can provoke an increase in blood pressure, even in borderline hypertensive and/or sensitive individuals. In most regards, our results are consistent with the animal and human studies reviewed, both those carried out with pure CO gas and those with cigarette smoke, in showing some degree of systemic arterial hypotension. The exceptions to this statement are the studies of human hypertensives, where cigarette smoking appears to exacerbate high blood pressure (*49,50,52–54*). This could be due to the fact that cigarette smoke contains many other substances in addition to CO to which some people may be especially sensitive.

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